THE EVOLUTION OF VIRULENCE AND EMERGING DISEASES

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ABSTRACT Insights into the evolution of virulence may aid efforts to control or even prevent emerging diseases. Specifically, dangerous pathogens can be distinguished from those that pose relatively little threat by identifying characteristics that favor intense exploitation of hosts by pathogens, hence causing high virulence. Studies to date have implicated several such characteristics, including transmission by vectors, attendants, water, and durable propagules. These insights may improve the return on investments in disease control by directing effort and resources to the most-dangerous emerging pathogens. The approach also should help us to identify those control measures that will guard against the future emergence of dangerous pathogens, even those that have not yet been identified.

One of the major goals of studying emerging disease organisms is to control and, if possible, prevent serious disease. Inasmuch as hundreds, perhaps thousands, of organisms can cause serious disease in humans, pessimists may say that this goal is hopeless. Optimists may say that it can be done if only we invest sufficient resources. I am pessimistically optimistic. I think that controlling the emergence of some kinds of disease organisms is virtually hopeless; however, we should be able to control some of the most-serious threats if we broaden our perspective to understand better the reasons why serious disease has occurred so commonly in the past. We then should be able to apply this understanding to enact policies that will allow us to recognize the major threats and focus on the subsets of these threats for which our efforts can be productive.

Even this more-modest goal will be challenging, but integration of insights from evolutionary biology can help us substantially in whittling down a seemingly overwhelming challenge into a more manageable one. Our greatest concern is with those disease organisms that are likely to be stably virulent in the human

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population over time. In using the term *stably virulent*, I refer to the number of people who will be affected negatively integrated over the duration of time during which an emergent disease will persist in the human population. The components of this concern are the harmfulness per infection, the prevalence of infection, and the persistence of this prevalence. A flare-up of a highly lethal disease in a few hundred people is not as much of a threat as the inexorable smoldering of a moderately lethal organism that can persist indefinitely, albeit less dramatically. The tuberculosis bacterium, in the broader analysis, is more dangerous to humans than the Ebola virus, even though Ebola in the hands of the media may make for a more sensational script.

FUNDAMENTAL QUESTIONS

This perspective on emerging diseases raises a critical question: Why do some disease organisms evolve toward a high, often lethal, virulence, whereas others, like the common cold virus, do not kill anyone, not even those who have compromised immune systems? There are two ways of approaching this question. The conventional approach is to try to understand the biochemical mechanisms that make one disease organism more severe than another. According to this conventional approach, one would say that the bacterium that causes cholera is often virulent because it produces a large amount of toxin, which in turn causes a large amount of fluid to rush into the lumen of the intestine from the cells that line the intestine. This fluid loss causes reduced blood volume, which then can cause shock and death. In evolutionary biology, such explanations are referred to as "proximate explanations" because they deal with the immediate mechanisms that cause the phenomenon. They comprise a perfectly valid and important class of explanations. For each proximate explanation in biology, however, there also exists a complementary "ultimate explanation," which considers why the characteristic has evolved. An ultimate explanation for cholera's virulence would consider how those organisms that produced a high amount of toxin might be superior competitively to those that produce less toxin. Such ultimate explanations of virulence thus focus on why organisms that possess a given level of virulence persist through time, even though other competing organisms with a different level of virulence presumably are being generated continually by mutations.

Having made this key distinction, we can ask a general ultimate question: Why are some disease organisms severe, while others are benign? We ask this question with the expectation that the answer will allow us to identify particular pathogens that confront us with the gravest long-term threat: pathogens that, if they get into the human population, may persist in a damaging state for a long period of time, pathogens like malaria, tuberculosis, and cholera.

EVOLUTIONARY MECHANISMS OF EMERGING INFECTIONS

René Dubos[1] wrote, "Given enough time, a state of peaceful co-existence eventually becomes established between any host and parasite." Evolutionary biologists recognize a problem with this conclusion. They think about characteristics like the inherent harmfulness of a disease organism in terms of the tradeoff between the benefits and costs that are associated with the characteristic. Pathogens accrue evolutionary benefits through increased replication of the genetic instructions for the characteristic. Costs typically are accrued through reductions in the transmission of the genetic instructions, for example, due to negative effects of host illness on pathogen transmission.

Evolutionary theory generally does not propose that virulence *per se* is beneficial. Rather, the logic begins by assuming that disease organisms, like any other kind of consumer, may benefit by exploiting their food supply, that is, their hosts. By exploiting its host, a disease organism is securing resources that it can use to reproduce and thereby contribute more copies of the instructions for that exploitation into future generations. If that were all there was to the association, disease organisms, like the pathogen in *The Andromeda Strain*, would be favored to eat us up. Something else is happening: the costs of virulence come into play. If a pathogen exploits its host increasingly, at some point the pathogen will make the host feel ill. If the illness makes the host immobile and if host mobility is necessary for transmission to new hosts, then that pathogen, although it might get more resources in the short run, will lose in the slightly longer run when it finds itself stranded with an ill or dead host.

This tradeoff deserves more-detailed examination because many well-educated people have been inculcated with the idea that benign coexistence is always the best evolutionary outcome for both host and parasite. It is an appealing notion, but some simple logic indicates that it is incorrect. Imagine a state of peaceful coexistence in which an organism that lives inside a host organism does not harm the host. What would happen if a variant appears that exploited that host a bit more? If that host did not feel ill, the new variant, by virtue of its more-exploitative nature, makes more copies of its exploitative instructions, which, as a result, displace the other instructions for the lower level of exploitation. Now, iterate this step until progressively more exploitative variants cause some disease. Will the exploitative variant win or will it not? The answer depends on how negatively the level of disease affects transmission. At some point, the critical threshold will occur: the increased benefits to the disease organism associated with the additional increment in exploitation are counterbalanced by the increased cost associated with transmission. At that point, natural selection no longer acts to increase the disease organism's exploitation of the host. This tradeoff argument is the framework for much of modern theory about the evolution of virulence.

Note, however, that this tradeoff considers what is best for the pathogen. The host, on the other hand, would benefit from having no disease. Host and parasite, therefore, often are fated to a continual coevolutionary race, with the host evolving immunological attributes such as somatic mutation and alteration of major histocompatibility antigens to reduce the exploitation by the pathogen; the pathogen evolves countermeasures to break through this control and move it closer to its optimum. As the pathogen gets closer to its optimum, the evolutionary pressure for a still closer approach diminishes. Similarly, as the host gets closer to elimination of disease, the evolutionary pressure for further purging of negative effects diminishes. The expected host-parasite association, therefore, will be bounded between the host's favored situation of no disease and the optimum for the pathogen here portrayed.

This argument presumes that host exploitation and virulence are linked. Researchers who focus on the specific variants sometimes dismiss theoretical arguments about the evolution of virulence by noting that they can find virulent mutants that do not derive any benefit from their virulence. Their mistake is the failure to realize that these virulent mutants generally are found as laboratory artifacts. If a pathogen in nature imposes a fitness cost on itself without providing a compensating benefit, it will tend to be eliminated by natural selection. We expect, therefore, that competition in nature will allow high virulence only if it is linked to some evolutionary benefit, such as the propagative benefits generated from increased exploitation of hosts.

If this approach to the evolution of virulence is valid, it should direct us to categories of pathogens that would be driven by natural selection to high levels of host exploitation and hence to high levels of virulence. It is this kind of understanding that should help us identify those pathogens that represent the greatest emerging threat of maintaining themselves indefinitely in a damaging way.

I have already suggested that host immobilization may impose important costs on pathogens by inhibiting transmission. An ill host does not move around as much as a healthy host, and if the pathogen relies on that mobility for transmission (as does, for example, the common cold virus), then the costs to the pathogen will rise relatively rapidly with increased host exploitation; consequently, natural selection should favor a relatively benign state of coexistence. But, some categories of disease organisms do not rely much on host mobility. Such organisms pay a relatively low price if their exploitation immobilizes the host. According to the tradeoff reasoning that I just have presented, pathogens in such categories should be particularly virulent. Some of these categories are discussed below.

TRANSMISSION BY ARTHROPOD VECTORS

One category involves transmission by arthropod vectors, such as mosquitoes. If a disease organism is mosquito borne, then it still can be transmitted even if a person is immobilized entirely with illness because mosquitoes come to feed from the ill person. In fact, experimental studies indicate that mosquitoes are better able to bite a laboratory animal when it is sick with a vector-borne disease such as malaria than when it is healthy. As a consequence, natural selection should ratchet up the level of exploitation for vector-borne pathogens, and we should see particularly high virulence among vector-borne diseases.

One problem with testing this idea involves quantifying virulence. Many symptoms may be defensive for the host. The investigator must identify some characteristic that is an indicator of the harm being done to the host. I have chosen death. Unlike other symptoms of illness, death is rarely interpretable as a defense against the parasite. Using death as an indicator does not imply that death is beneficial to the parasite. Rather, it presumes only that probabilities of death are an indicator of harmfulness.

The mortality associated with untreated infections is highly variable for both vector-borne and directly transmitted pathogens, but it is greater for vector-borne pathogens than for directly transmitted pathogens. This difference is illustrated in Fig. 1 for vector-borne pathogens and respiratory tract pathogens of humans. This association suggests part of the ultimate explanation for the question: Why do some pathogens cause more harm than others? If a pathogen is borne by a vector, natural selection apparently favors a relatively high level of host exploitation and hence host damage.

Most pathogens of the respiratory tract fall into the mildest category: less than 1 death in 10,000 infections (the left-most category in Fig. 1). Yet, some, such as the smallpox virus and the tuberculosis bacterium, are regularly lethal. If we are concerned about emerging disease organisms that are likely to be maintained stably with high virulence, obviously we cannot restrict our attention to vector-borne pathogens. We need to know why some pathogens of the human

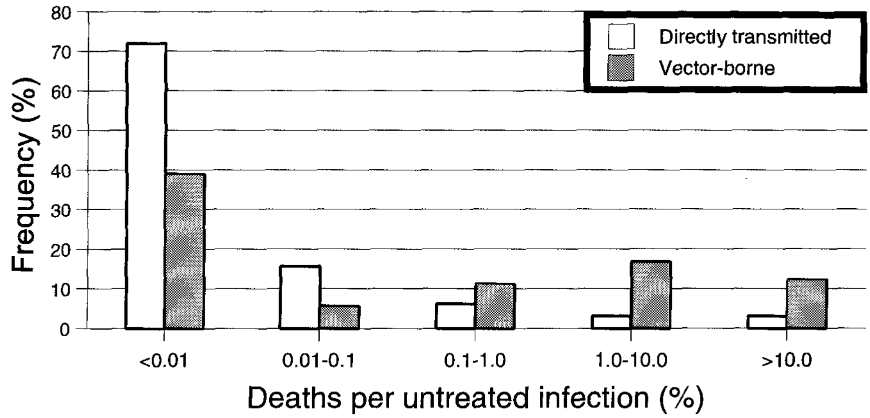

FIG. 1 Lethality of vector-borne and directly transmitted pathogens in untreated infections. Pathogens are restricted to those that are transmitted regularly to and from humans. Frequencies correspond to percentages of species in each category (for other details, see Ref. 2).

respiratory tract are so virulent. Is there something about the smallpox virus or tuberculosis bacterium that has allowed them to be maintained with high virulence over time?

SIT-AND-WAIT TRANSMISSION

There are two ways by which a disease organism can go from an immobilized infectious host to a susceptible host. One is by relying on something mobile, like a mosquito, to transfer it. The other way is to rely on the mobility of susceptible individuals that come to the place where a pathogen has been released from an immobilized infectious individual. Pathogens can exploit the mobility of uninfected hosts for transmission if the pathogens are durable in the external environment. If, for example, a disease organism could remain viable for 10 years after being released from its last host, consider how many susceptible hosts might come to the spot at which they were released. Some insect pathogens, such as nuclear polyhedrosis viruses and the bacterium *Bacillus larvae*, are extremely durable, surviving many years, decades, or perhaps even centuries in their resistant forms.[3,4] They also tend to turn their hosts into soup.[5–7]

Something similar might be responsible for the variation in virulence of directly transmitted pathogens illustrated in Fig. 1. To evaluate this hypothesis, Bruno Walther and I reviewed the data available in the literature to assess whether the more-durable respiratory tract pathogens are more lethal. Our test encompassed all bacteria and viruses that were primarily pathogens of the human respiratory tract. We found that durability was associated significantly with mortality per untreated infection.[8] The most-durable respiratory tract pathogens include the smallpox virus and the tuberculosis bacterium. The least durable include the rhinoviruses that cause the common cold.

Therefore, data from vector-borne and respiratory tract pathogens of humans improve our ability to recognize pathogens that could be particularly dangerous once they have emerged. If a disease organism has just begun to emerge and it is durable or vector borne, it warrants special concern because it is in a category of organisms with a proven ability to maintain virulence over time. An emerging vector-borne disease may have the potential to be another malaria or yellow fever. An emerging durable pathogen may have the potential to become another tuberculosis bacterium or smallpox virus.

CULTURAL VECTORS: ATTENDANT-BORNE AND WATERBORNE TRANSMISSION

Pathogens can evolve rapidly in response to human activities. In hospitals, for example, antibiotic resistance can evolve within a few weeks if enough antibiotics are applied and if the relevant genetic instructions are present, but I think we have been focused too narrowly on antibiotics in our discussions of the problems raised by evolutionary responses of disease organisms to human activities. Although antibiotic resistance is very important, it may not be as fundamentally important as virulence. Antibiotic resistance is damaging only if it is linked to virulence. Why restrict our attention to the evolution of antibiotic resistance in response to human activities when the evolution of a pathogen's virulence is arguably more important?

Some of our activities, along with certain aspects of our cultures, provide analogs of arthropod vectors and may facilitate transmission of durable pathogens. I refer to these analogs as "cultural vectors." In hospitals, for example, pathogens can be transmitted from immobile infected individuals via the hands of attendants. If a baby is infected with a diarrheal organism such as *Escherichia coli* and that organism is reproducing extensively, attendants are likely to spread the organism even if they are being fairly careful. With greater exploitation ol the babies by the bacterium, there should be greater densities of organisms shed in the diarrheal stools and a greater likelihood of contamination. It is easy to picture how attendants in hospitals could have an evolutionary effect that mosquitoes have in nature. Because mobility of the infected host is no longer important for transmission, organisms that exploit their hosts beyond the threshold of immobilization do not pay a large price for this exploitation. If this idea is correct, we should see some disturbing trends in hospitals. One such trend should be an association between the duration of attendant-borne cycling and virulence. Such data are difficult to obtain, but a considerable amount of data were accumulated during the window of time between the first recognition of *E. coli* as a major cause of infantile diarrhea and the widespread use of effective antibiotics against it. These data from hospital outbreaks of *E. coli* show that, as the duration of outbreaks increased (beyond 15 months for some outbreaks), the deaths per infection increased (Fig. 2).

If the increased lethality resulted from increased virulence, it is not critical whether the variation in virulence was generated *de novo* in the hospital environment or whether the harmful variants entered from the outside and were better able to persist in an environment with a great potential for attendant-borne transmission. Either way, the potential for attendant-borne transmission would have been responsible for increased virulence in the hospital environment. Data for other bacteria responsible for hospital outbreaks also are consistent with an association between attendant-borne transmission and increased virulence.[11,12] The data from hospital outbreaks suggest that, if we are concerned about the emergence of dangerous pathogens, we should pay close attention to hospital environments because particularly virulent variants may have a selective advantage in these environments. The concern is all the more pressing in light of the seemingly inexorable development of antibiotic resistance in hospital environments.

The evolutionary interpretation of the hospital data raises the possibility of controlling virulence by controlling its evolution. This evolutionary approach suggests that certain interventions will have greater long-term payoff relative to others than has previously been appreciated. Specifically, a greater investment in improving those hygienic standards that reduce attendant-borne transmission not only may reduce the frequencies of infection, but also may reduce the harmful-

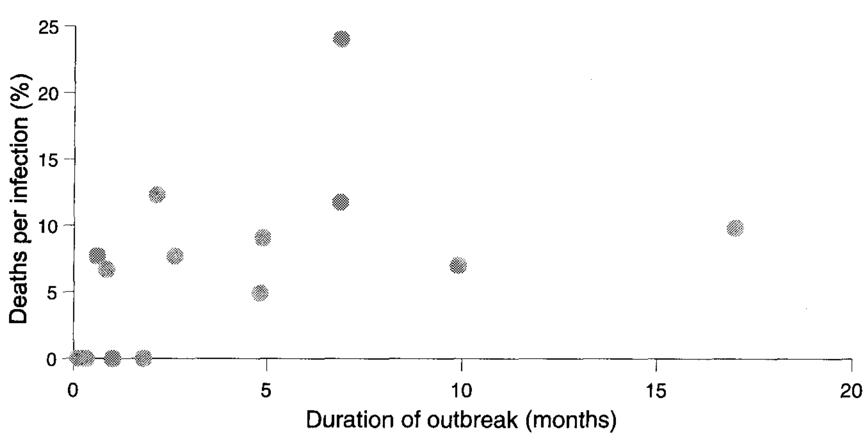

FIG. 2 Duration and mortality of hospital outbreaks of *Escherichia coli* (for other details, see Refs. 9 and 10).

ness per infection. Now that many hospital strains are resistant to antibiotics, resolution of this issue seems more pressing than ever. By controlling the damage with less reliance on antibiotics, we may slow the development of antibiotic resistance. If strains are already resistant to antibiotics, we may recognize a control measure that is more effective than previously thought at a time when effective control measures are needed desperately.

The possibility of evolutionary control of virulence also seems to be particularly applicable to another category of diseases: diarrheal diseases that are transmitted though fecally contaminated water. As is true of pathogens transmitted by means of biting arthropods and attendants within hospitals, waterborne transmission allows diarrheal pathogens to be transported from immobilized infected hosts to uninfected hosts. In an area where water supplies are not protected, a person with incapacitating diarrheal illness will release the diarrheal pathogens into clothes and bed sheets, which will be removed by attendants and washed in bodies of water such as canals, rivers, or lakes. People may come to the body of water to obtain drinking water, or the wash water may drain into supplies of drinking water. Either way, the cycle is completed when susceptible individuals drink the contaminated water. Even though the infected individual is not mobile, thousands of susceptible individuals could be infected by that individual as a result of this combination of waterborne and attendant-borne transmission. Like attendant-borne transmission in hospitals, this process is the cultural analog of a biological vector, that is, a cultural vector. It is like a horde of mosquitoes transporting pathogens from the immobilized individual to susceptible individuals.

This hypothesized effect of waterborne transmission has been tested in a way analogous to the tests I have mentioned already. Specifically, I examined the literature to determine whether the lethality of bacterial agents of human diarrhea is correlated positively with the degree to which they are waterborne. Figure 3 shows that the correlation exists. Topping the list is the classical cholera organism, which in the absence of treatment, would kill approximately 15% of the people it infects. The agent of typhoid fever and the most severe of the agents of bacterial dysentery also often are waterborne and also are among the most-severe diarrheal pathogens.

CONCLUSION

None of the studies that I have presented is the final word. They represent a beginning rather than an end, the beginning of an ongoing synthesis of evolutionary biology with epidemiology and public health. The studies offer a collection

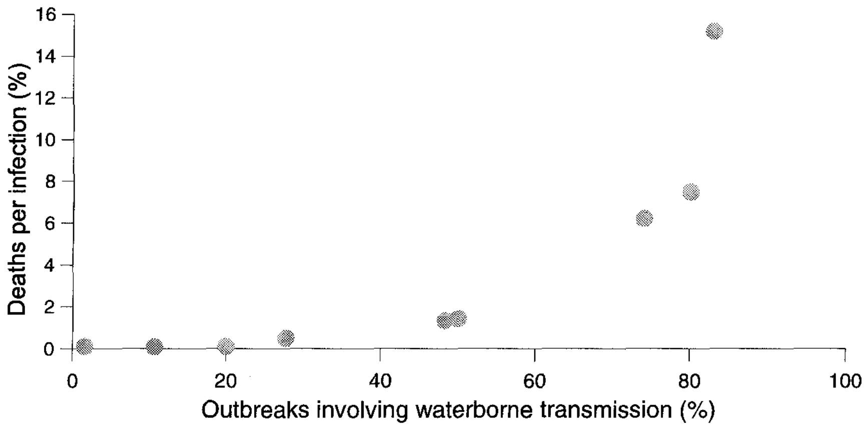

FIG. 3 Waterborne transmission and mortality of diarrheal bacteria of humans. Pathogens ordered from most to least waterborne are classical *Vibrio cholerae, Shigella dysenteriae* type 1, *Salmonella typhi*, el tor *V. cholerae, Shigella flexneri, Shigella sonnei*, enterotoxigenic *E. coli, Campylobacter jejuni*, and nontyphoid *Salmonella* (for other details, see Ref. 13).

of ultimate explanations for the observed variability in pathogen virulence. These ultimate explanations contrast with those one would draw based on the traditional view that disease organisms evolve toward peaceful coexistence. According to that view, the current variation would represent variation in the stages of host/parasite coadaptation, with the particularly harmful parasitisms representing states of poor coadaptation. Because the studies to date have substantial explanatory power, they justify further studies designed to distinguish among alternative explanations. More to the point with regard to emerging diseases, however, the findings specify some pathogens that are particularly dangerous and draw attention to additional information that needs to be obtained for assessment of others.

When the danger of a pathogen is being assessed, certain questions must be answered. Is the pathogen transmitted by a vector? Is it durable in the external environment? Is it transmitted by attendants? Is it transmitted by water? A final question pertains to a separate category of tradeoffs that is addressed elsewhere[11,14]: Is it sexually transmitted with any tendencies toward being invasive, mutation prone, or oncogenic? If the answer to any of these questions is "yes," then we should pay the organism special attention.

If the answers are not available, they need to be obtained. We may need to invest our disease-control resources differently, to find out, for example, how durable a newly identified disease organism is in the external environment. Although knowledge about pathogen characteristics is imperfect, the knowledge we have suggests that many of the disease organisms that capture our attention will be much less serious over the long run than others. Ebola virus, for example, has a mix of characteristics that are unlikely to allow it to persist stably with its characteristically high virulence in human populations (although we could use more information about its durability under various environmental conditions). We can expect, instead, that it sporadically will cause nasty, but localized, outbreaks involving a few hundred people before burning itself out. The considerations raised here suggest that Rift Valley fever virus is overall a more dangerous pathogen. Being vector borne with sufficient virus density in the blood for human-mosquito-human transmission, it has a mix of characteristics that could allow it to persist stably in humans if the mosquito density is sufficient. If left unchecked, it poses a threat more like yellow fever than Ebola.

This presentation has focused on the usefulness of an evolutionary perspective for identifying pathogens that pose a particularly great threat to humans. Another, perhaps more important, evolutionary consideration asks whether this knowledge could enable us to prevent these organisms from becoming dangerous in the first place. I think it can.

Consider waterborne transmission. By introducing clean water supplies, we should be able to prevent those organisms that we have identified as waterborne from spreading. The milder competitors should spread instead. This shift, in fact, has happened in the case of the dysentery bacteria of the genus *Shigella*. In New York City and throughout the US and the world, as fecal contamination of water supplies has been eliminated, the composition of *Shigella* has turned like clockwork in favor of the most-benign species. By cleaning up water supplies, we should be able to keep the known virulent diarrheal organisms from emerging and causing pandemics. Even more importantly, we should be preventing the emergence and spread of new variants that have not yet been identified and even may not have originated yet. If the ideas presented here are correct, we do not necessarily have to wait for the time lags between the occurrence of a new threat, recognition of the threat, and enactment of control measures. Putting in place the infrastructure that disfavors the virulent variants may control the problem before we recognize it, even if we never recognize it and perhaps even before it occurs, because virulent variants may never have the chance to generate the stepping stones of genetic change toward increased virulence. This argument helps us understand why we have not had major outbreaks of severe diarrheal disease in the US and other countries since the introduction of clean water supplies during the first half of the 20th century. Outbreaks of typhoid, cholera, and dysentery were prevalent before then and have continued in places with poor water supplies. Plenty of cases have been imported, but these imported cases fizzle on their own (*e.g.*, for the most harmful type of *Shigella*, see Weissman and colleagues[15]). This kind of increased efficiency in disease control through infrastructural improvements should give us a much bigger bang for each buck of investment, whether that investment is in improving bad water supplies or improving aging water supplies. More generally, this approach to the control of emerging diseases can be thought of as the ultimate in preventive medicine: it not only prevents people from getting infected by disease organisms that threaten them at the moment, but it also should prevent the disease organisms from evolving those threatening characteristics in the first place.

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